Journal of Dementia

DNMT1 overexpression in neurons results in dysregulation of genes associated with Alzheimer's and Parkinson's Disorders

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Abstract

DNA methylation is an epigenetic modification of mammalian genomes that plays an important role in cell differentiation and normal development. This epigenetic modification is mediated by DNA methyltransferases (DNMTs) of which DNMT1 is a maintenance methyltransferase. Abnormalities in DNA methylation patterns as well as dysregulation of DNMTs have been reported in many disease conditions. In the context of Alzheimer's disease (AD), two recent studies showed increased levels of DNMT1 transcripts correlated with APOE polymorphisms and increased expression of DR4 that promotes apoptosis and neurodegeneration. However, it is not clear whether there is dysregulation of any other AD-associated genes due to DNMT1 overexpression. Towards this goal, we performed transcriptome sequencing of DNMT1-overexpressing neurons derived from *Dnmt1*$^{tet/tet}$, a transgenic mouse embryonic stem cell line (ESC). Of the 2,463 dysregulated genes associated with neurological disorders, 939 were associated with AD and Parkinson's disease (PD). Sixty-six were common to both disorders and were studied further to understand the relationship between dysregulation and DNA methylation levels. Reduced Representation Bisulfite Sequencing (RRBS) analysis of the *Tet/Tet* neurons suggested that many of the dysregulated genes showed either no change in methylation or hypomethylation, but not hypermethylation, suggesting absence of clear correlation between methylation changes and gene expression. Bioinformatic analysis of the 939 genes revealed that signaling pathways regulating pluripotency, serotonergic synapse, HIF-1 and Axon guidance were affected in the *Tet/Tet* neurons. Importantly, the *Tet/Tet* ESCs showed defective neurogenic potential, a phenotype recently reported in AD and other neurological disorders. These results suggest that (i) DNMT1 overexpression is a potential etiological factor for neurodegenerative disorders such as AD and PD, (ii) Dysregulation of AD- and PD-associated genes was independent of catalytic activity of DNMT1 and (3) The mechanism by which DNMT1 overexpression results in dysregulation of AD- and PD-associated genes remains unclear.

Biography

Mohan KN has completed his Ph.D. at the age of 30 years from Indian Institute of Science, Bengaluru, India. He is an Associate Professor of BITS Pilani, India. He has over 25 publications that have been cited over 450 times and his publication H-index is 10 and has been serving as an invited reviewer of reputed Journals.

5th Annual Summit on Dementia and Alzheimer's Diseases | September 25, 2020

Citation: Mohan KN, DNMT1 overexpression in neurons results in dysregulation of genes associated with Alzheimer's and Parkinson's Disorders, Dementia Congress 2020, 5th Annual Summit on Dementia and Alzheimer's Diseases, September 25, 2020, Page No-01